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(54) Tablet for extended release of a drug in the stomach

(57) The invention relates to a tablet for extended release of a drug in the stomach, comprising granules of said drug in a hydrophilic matrix, said granules being coated with a coating comprising a source of a carbon dioxide and said coating granules being blended with an agent inducing the release of carbon dioxide and (a) tabletting aid(s).

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Description

[0001] Chronic illness is often treated with medication that involves multiple daily doses of a particular therapeutic entity. Patient compliance and therefore efficacy of therapy, may be improved by use of an extended release formulation, for example a hydrophilic matrix tablet that allows once daily dosing of medication.

[0002] The rational design and evaluation of effective extended release delivery systems needs to take into account several parameters:

(1) the delivery system,
(2) physicochemical properties of the drug, and
(3) physiological considerations.

[0003] Each of these is inter-related to the other two and affects the rate at which the drug is absorbed throughout the GI tract and its ultimate bioavailability and pharamcokinetic profile. These three parameters are considered below.

(1) The range of delivery systems available for the controlled/extended release of drugs is huge. In summary, the nature of the delivery system will be dictated by the properties and dose of the drug, desired release profile and physiological factors. For example, it would prove challenging to develop an extended release system for a high dose, water soluble drug with a narrow absorption window limited to either the stomach and/or the upper intestine as defined by its pKa or site of active transport mechanism.
(2) The physicochemical properties of a drug will affect its absorption through the GI tract. Many drugs are, or are the salts of weak bases or weak acids, and as such demonstrate pH dependent solubility. An extension of this theory is the pH partition hypothesis which asserts that the passage rate of a drug through a membrane is dependent on the environment pH and pKa of the drug. Drugs with low pKa (3-7) are non ionised in the stomach and subsequently rapidly absorbed. On passage to the small intestine with comparatively increased pH, the rate of ionisation is changed and absorption subsequently slowed. The converse is true for drugs with higher pKa values.
The stability of the drug through the pH range of the GI tract must also be considered.
(3) Physiological considerations include pH of the environment, the effect of gastric emptying time and variation of GI transit time. The pH is considered in (2). The effect of gastric emptying in the process of drug absorption is well documented.

[0004] Once an extended release dosage form passes beyond its principle absorption site in the GI tract, any further drug released may not contribute to therapy.

[0005] Factors which affect gastric emptying of the delivery system include fed or fasted state and the size of the delivery system.

[0006] The present invention provides formulations for drugs, in particular hydrophilic drugs, which have a narrow window of absorption, limited predominantly to the stomach or the upper intestine as limited by their low pKa value (3-7) and/or their site of active transport absorption mechanism, but which require an extended release mechanism in order to (i) achieve a desired pharmacokinetic or bioavailability profile, (ii) overcome saturation of the active transport absorption mechanism and (iii) to overcome/reduce GI side effects due to the bolus release of the drug.

[0007] Furthermore, the present invention accomodates high dosage, highly soluble drugs in the formulation, allowing up to a 90% drug loading, thus minimising overall dosage unit weight/size and improving patient acceptability and compliance.

[0008] Furthermore, the formulation of the present invention has been designed in such a way as to allow optimum stability of the active component. It separates the active drug from acid and alkaline components in the formulation whilst allowing the formulation to maintain its novel behaviour.

[0009] The present invention relates to a floating extended release hydrophilic matrix formulation. The floating mechanism enables the delivery system to be maintained in the stomach for up to 4 hours, thus allowing optimum drug absorption as defined above, and maintaining an extended release of the drug to achieve desired pharmacokinetic and bioavailability profiles whilst reducing side effects. The claims are supported by pharmacoscintographic and pharmacokinetic studies to assess bioequivalence of a model active substance.

[0010] This invention can advantageously be applied to metformin.

[0011] Metformin hydrochloride has been successfully used for many years in the treatment of non insulin dependent diabetes.

[0012] Metformin is commercially available as 500 or 850 mg coated tablets. The usual posology is 500 mg every 8 hours or 850 mg every 12 hours, this posology is then adapted according to the biological results, to a maximum of 3 g daily in divided dose. At the beginning of the treatment, metformin may induce gastro-intestinal side effects such as diarrhoea and nausea.

[0013] Previous pharmacokinetic studies with oral metformin indicate that it has a narrow window of absorption at the upper part of the small intestine with a bioavailability of approximately 50%. This low bioavailability is thought to be due to a dose dependent saturation of receptors.

[0014] The present invention provides a new dosage form of metformin which will decrease the gastro-intestinal side effects at the beginning of the treatment and improves the bioavailability by sustaining the drug release in the stomach and optimising receptor uptake in the upper intestine.

SUMMARY

[0015] The present invention relates to a floating extended release hydrophilic matrix formulation, in particular tablets, for the extended release of a drug, and to a process for their preparation.

[0016] The present invention relates to a tablet for extended release of a drug, in particular a hydrophilic drug, in the stomach, comprising granules of said drug in a hydrophilic matrix, said granules being coated with a coating comprising a source of a carbon dioxide and said coated granules being blended with an agent inducing the release of carbon dioxide and (a) tabletting aid(s).

[0017] The present invention relates in particular to tablets for the sustained release of any hydrophilic drugs with (i) a narrow absorption window limited to the stomach or upper GI and (ii) a low pKa value (3-7), whose bioavailability could be improved by sustained absorption in the upper GI, for example benzodiazepines (e.g. diazepam, chlordiazepoxide, nitrazepam), NSAIDs (e.g. indomethacin, naproxen, ibuprofen, fenoprofen), some antibacterials (e.g. sulphadiazine, isoniazid, flucloxacillin, ciprofloxacillin), metoprolol, minoxidil hydralazine, methotrexate, aminophylline, chlorpromazine, fluphenazine, cimetidine, ranitidine, metformin, local anaesthesics (e.g. benzocaine), contrast media (e.g. barium sulphate) or any salts thereof.

[0018] The tablet according to the present invention may be obtained by a process comprising :

a) forming drug granules by wet granulation of a mixture of the hydrophilic drug and 2-hydroxypropylmethylcellulose ;
b) coating these granules with bicarbonate and binder ;
c) blending the coated granules with a tabletting aid and an organic acid and,
d) tabletting the blend thus obtained into tablets, said 2-hydroxypropylmethylcellulose forming a hydrophilic matrix capable of retaining carbon dioxide which is formed when the tablet is administrated.

[0019] In general the concentration of the drug may be 10 to 90 % by weight of the tablet.

[0020] Thus the tablets of the present invention may contain :

10 to 90% by weight of drug,
5 to 25 % by weight of 2-hydroxypropylmethylcellulose,
3 to 25 % by weight of bicarbonate,
1 to 10 % by weight of an organic acid,
0.5 to 30 % by weight of tabletting aid.

[0021] The 2-hydroxypropylmethylcellulose is a material which is able to form a hydrophilic matrix capable of retaining carbon dioxide formed when, in the stomach of the patient, the organic acid reacts with the bicarbonate.

[0022] Examples of appropriate grades of 2-hydroxypropylmethylcellulose are those having a methoxy range of 19 to 32 % by weight, a hydroxypropyl range of 4 to 12 % by weight and a viscosity of 15.10^{-3} Pa.s to 100 Pa.s in a 2 % aqueous solution at 20° C. The 2-hydroxypropylcelluiose is preferably a polymer having a methoxy range of 19 to 24 % by weight, a hydroxypropyl range of 7 to 12 % by weight and a viscosity of about 100 Pa.s in a 2 % aqueous solution at 20° C. Such a grade is named HPMC 2208 under the USP specifications and is available under the name Methocel K100M.

[0023] Advantageously the mixture used for forming the granules comprises a granulating binder. This granulating binder is in particular a polyvinylpyrrolidone such as for example, a polyvinylpyrrolidone having a molecular weight of 45 000. The polyvinylpyrrolidone may be used in a proportion of 0.5 to 10 % with respect to the final tablet.

[0024] After the granulating step the granules may be sieved and dried. They are advantageously extruded and dried The extrusion provides granules in the size range of 0.35 to 1.4 mm.

[0025] The granules are then mixed with the bicarbonate and a binder.

[0026] The source of carbon dioxide is in particular a bicarbonate of an alkali metal such as sodium or potassium carbonates or bicarbonates or sodium glycine carbonate. Sodium bicarbonate is the preferred source of carbon dioxide.

[0027] The binder used for coating with bicarbonate may be any binder usually used in order to increase the coating spreading efficiency of a powder on granules. This binder on the periphery of the granules will also facilitate the compression. This binder may be a polyvinylpyrrolidone such as PVP K30 (having a molecular weight of 45 000) or a 2-

hydroxypropylmethylcellulose having a methoxy content of 28-30 % by weight, a hydroxypropyl content of 7-12 % by weight and a viscosity of 12-18.10^{-3} Pa.s, such as Methocel E15 LV.

[0028] This binder may be used in a proportion of 1 to 5 % by weight.

[0029] The coated granules are then blended with a tabletting aid and an organic acid.

[0030] The tabletting aid may be any aid usually used for making tablets. This aid is for example magnesium stearate.

[0031] Agents that induce the release of carbon dioxide are preferably pharmaceutically acceptable organic acids e.g. tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, ascorbic acid, maleic acid or preferably citric acid.

[0032] The tablets thus obtained may then be coated with a hydrophilic cellulose polymer and talc. The hydrophilic cellulose may be a 2-hydroxypropylmethylcellulose having a methoxy content of 28 to 30 % by weight, a hydroxypropyl content of 7 to 12 % and a viscosity of 12 to 18.10^{-3} pa.s as measured in a 2 % aqueous solution at 20° C.

[0033] For example the final coating of the tablet may comprise 0.5 to 5 % of said 2-hydroxypropylmethylcellulose such as Methocel E15 LV and 0.05 to 0.5 % of talc, said percentages being calculated with respect to the non-coated tablet.

EXAMPLE 1

[0034] A tablet of metformin having the following composition has been prepared:

Ingredients	mg/tablet	Weight percentage
Metformin hydrochloride	500	62.42
Methocel K100M	127.5	15.9
PVP K 30	36.9	4.6
SPRAY		
PVP K 30	13.25	1.6
Sodium bicarbonate	96.4	12
Extragranular phase		
Citric acid	17.15	2.1
Magnesium stearate*	9.8	1.22

* A proportion of the magnesium stearate may be incorporated intragranularly if necessary.

[0035] The tablets are prepared as follows :

a) Granular stage

[0036] The metformin and Methocel K 100 M are blended in a suitable mixer.

[0037] The PVP K 30 solution is then added to the powder blend while granulating.

[0038] The wet powder is then extruded through a suitable screen, before being dried in a fluid bed dryer.

b) Bicarbonate spraying stage

[0039] A bicarbonate/PVP solution is sprayed on the dry granules using a fluid bed coater.

c) Compression stage

[0040] The dry sprayed granules are now blended with citric acid and with magnesium stearate in a suitable mixer.

[0041] The final blend is then compressed into tablets.

EXAMPLE 2

[0042] A tablet of metformin having the following composition has been prepared:

Ingredients	mg/tablet	Weight percentage
Metformin hydrochloride	500	68.77
Methocel K 15M	50.56	6.94
Methocel E 4M	11.84	1.63
PVP K 30	36.9	5.0
SPRAY		
Methocel E 15 LV	13.25	1.8
Sodium bicarbonate	96.4	13.26
Extragranular phase		
Citric acid	7.7	1.06
Magnesium stearate*	10.35	1.42

* A proportion of the magnesium stearate may be incorporated intragranularly if necessary.

[0043] The tablets are prepared as follows :

a) Granular stage

[0044] The Metformin, Methocel K 15 M and Methocel E 4 M100 are blended in a suitable mixer.
[0045] The PVP K 30 solution is then added to the powder blend while granulating.
[0046] The wet powder is than extruded through a suitable screen, before being dried in a fluid bed dryer.

b) Bicarbonate spraying stage

[0047] A bicarbonate/Methocel E 15 LV solution is sprayed on the dry granules using a fluid bed coater.

c) Compression stage

[0048] The dry sprayed granules are now blended with citric acid and with magnesium stearate in a suitable mixer.
[0049] The final blend is then compressed into tablets.

Claims

1. A tablet for extended release of a drug in the stomach, comprising granules of said drug in a hydrophilic matrix, said granules being coated with a coating comprising a source of a carbon dioxide and said coating granules being blended with an agent inducing the release of carbon dioxide and (a) tabletting aid(s).

2. A tablet as claimed in in claim 1, wherein the drug is a hydrophilic drug.

3. A tablet as claimed in claim 2, said tablet being obtained by :

   a) forming drug granules by a wet granulation of a mixture of a hydrophilic drug and 2-hydroxypropylmethylcellulose ;
   b) coating these granules with bicarbonate and a binder,
   c) blending the coated granules with a tabletting aid and an organic acid, and
   d) tabletting the blend thus obtained into tablets,

   said 2-hydroxypropylmethylcellulose forming a hydrophilic matrix capable of retaining carbon dioxide which is formed when the tablet is administered.

4. A tablet as claimed in claim 1 or 2, wherein the drug is selected from benzodiazepines, NSAIDs, antibacterials, metoprolol, minoxidil, hydralazine, methotrexate, aminophylline, chlorpromazine, fluphenazine, cimetidine, ranitidine, metformine, local anaesthesics, constrat media and salts thereof.

5. A tablet as claimed in claim 2 or 3 wherein the hydrophilic drug is a salt of metformin, e.g. metformin hydrochloride.

6. A tablet as claimed in anyone of claims 2 to 4 comprising :

10 to 90% by weight of drug,
5 to 25% by weight of 2-hydroxypropylmethylcellulose,
3 to 25% by weight of bicarbonate,
1 to 10% by weight of an organic acid,
0.5 to 30% by weight of a tabletting aid.

7. A tablet as claimed in anyone of claims 2 to 6 comprising polyvinylpyrrolidone as binder for the coating with bicarbonate.

8. A tablet as claimed in claim 7 comprising 1 to 5% of polyvinylpyrrolidone.

9. A tablet as claimed in anyone of claims 2-8 wherein the 2-hydroxypropylmethylcellulose has a methoxy range of 19 to 32% by weight, a hydroxypropyl range of 4 to 12% by weight and a viscosity of 15.10^{-3} Pa.s to 100 Pa.s in a 2% aqueous solution at 20° C.

10. A tablet as claimed in claim 9 wherein the 2-hydroxypropylmethylcellulose has a methoxy range of 19 to 24% by weight, a hydroxypropyl range of 7 to 12% by weight and a viscosity of about 100 Pa.s in a 2% aqueous solution at 20° C.

11. A tablet as claimed in anyone of claims 2 to 10 comprising a coating of a hydrophilic cellulose polymer and talc.

12. A process for preparing a tablet as claimed in claim 3, comprising :

a) forming hydrophilic drug granules by a wet granulation of a mixture of the hydrophilic drug and 2-hydroxypropylmethylcellulose ;
b) coating these granules with bicarbonate and a binder,
c) blending the coated granules with a tabletting aid and an organic acid, and
d) tabletting the blend thus obtained into tablets.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 98 40 1956

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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12-01-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0235718 A	09-09-1987	JP 62195323 A	28-08-1987
		CA 1288697 A	10-09-1991
		DE 3774148 A	05-12-1991
		ES 2051698 T	01-07-1994
		GR 3003031 T	17-02-1993
		US 4844905 A	04-07-1989
EP 0455475 A	06-11-1991	AT 124626 T	15-07-1995
		AU 645555 B	20-01-1994
		AU 7596891 A	07-11-1991
		CA 2041400 A	04-11-1991
		DE 69110969 D	10-08-1995
		DE 69110969 T	16-11-1995
		DK 455475 T	30-10-1995
		GB 2243549 A,B	06-11-1991
		IE 65826 B	15-11-1995
		US 5286492 A	15-02-1994
EP 0283369 A	21-09-1988	FR 2611500 A	09-09-1988
		AU 610134 B	16-05-1991
		AU 1272788 A	08-09-1988
		CA 1328606 A	19-04-1994
		DE 3886075 D	20-01-1994
		DE 3886075 T	14-04-1994
		DK 116788 A	07-09-1988
		JP 2108355 C	06-11-1996
		JP 8018978 B	28-02-1996
		JP 63230628 A	27-09-1988
		ZA 8801540 A	26-08-1988